November 28, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2005N-0311: Critical Path Initiative; Developing Prevention Therapies; Planning of Workshop; Request for Comments

Novartis Pharmaceuticals Corporation ("Novartis") is an affiliate of Novartis AG, a world leader in pharmaceuticals and consumer health. Novartis researches, develops, manufactures, and markets leading innovative prescription drugs used to treat a number of diseases and conditions, including central nervous system disorders, organ transplantation, cardiovascular diseases, dermatological diseases, respiratory disorders, cancer, and arthritis.

Novartis is submitting these comments regarding proposed topics for discussion at the upcoming workshop on chemoprevention therapies in response to the Agency's request for comments published in the Federal Register on August 3, 2005. It is Novartis' position that chemoprevention therapies represent an important advancement in public health through the prevention of disease and reduction of risk of illness. Novartis supports the Agency's efforts in pursuing Critical Path initiatives and welcomes the opportunity to provide input on the content of this workshop.

Novartis agrees with many of the topics for discussion recommend by the Agency. The following comments reflect the topics Novartis believes would be particularly valuable for discussion during this workshop.

1) Definition of Chemoprevention Terminology

The field of preventive medicine has evolved over the past several decades. Today, chemoprevention terminology is used widely by many medical specialties in reference to diseases that are diagnosed and treated in the practice of medicine. The topic of chemoprevention has moved beyond medical circles and has become an important component of discussions concerning health and quality of life. Prevention is a central topic of professional publications such as the *Journal of Clinical Epidemiology* and the *American Journal of Preventive Medicine*, as well as lay magazines such as *Prevention*.

Novartis recommends that the workshop begin with a discussion of the terminology associated with preventive medicine to ensure a common understanding of key terminology. The Agency might consider gathering information (possibly via a survey)

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concerning definitions commonly employed by different stakeholders in advance of the workshop. The results of this research could be presented and discussed at the conference.

Suggested items to be included in a discussion of chemoprevention terminology are as follows:

a) Review of the definitions of primary, secondary and tertiary prevention. For instance, in a clinical setting, suggested definitions include the following[1]:

   i) **Primary preventive measures**- those provided to individuals to prevent the onset of a targeted condition, e.g., routine immunization of healthy children.

   ii) **Secondary preventive measures**- those aimed at identifying and treating asymptomatic persons who have already developed risk factors, but in whom the condition has not become clinically apparent, e.g., screening for high blood pressure.

   iii) **Tertiary preventive measures**- those interventions aimed at treating and managing clinically significant abnormalities in patients with established related conditions, e.g., insulin therapy to prevent complications of diabetes mellitus.

b) Adaptation of the definitions above to different therapeutic areas, e.g., oncology, cardiology and metabolic disease.

2) Lessons Learned that May Impact the Development of Future Chemoprevention Therapies

Several chemoprevention therapies have been developed over the years such as cholesterol-lowering agents and antihypertensives. Novartis recommends that FDA initiate a discussion of the lessons learned in the development of these and other therapies. Understanding the successes and failures of past chemoprevention programs is essential to the development of future programs.

Suggested topics for a discussion of the lessons learned that may impact the development of future chemoprevention therapies are as follows:

a) The regulatory and policy issues that impacted development of the therapy

b) Development and validation of endpoints (e.g. surrogate, composite)

c) Trial designs utilized in these programs

d) Strength of evidence necessary to gain approval

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[1] In: AAVV: *Guide to Clinical Preventive Services. Report to the U.S. Preventive Services Task Force, 2nd Edition, William & Wilkins, Baltimore, 1996, p. xii*

3) Clinical Trial Designs

Innovative study design solutions will be key to addressing some of the multifaceted complexities of chemoprevention trials. Suggested topics for a discussion of clinical trial design include the following:

a) Composite endpoints (more than one type of event)

b) Adaptive trial designs

c) Factorial trial designs to test more than one chemoprevention therapy

d) Controlled vs. uncontrolled

e) Disease specific vs. global endpoints

f) Use of meta-analyses and observational studies

4) Characterization of the Appropriate Patient Population to Optimize Benefit-Risk

The ability to distinguish and identify patients at risk is essential to successful outcomes in chemoprevention trials. Suggestions for a discussion on the characterization of the appropriate patient population to optimize benefit and risk include the following:

a) Identifying the appropriate patients

b) Identifying those at highest risk

   i) Tools
   ii) Screening process and algorithms
   iii) Healthcare costs

5) Potential for New Regulatory Pathways

As chemoprevention outcomes data may take many years to collect, it is important to look at innovative pathways for regulatory approval of chemoprevention therapies that could bring such products to the market sooner. One suggestion would be to consider adopting a model similar to the accelerated approval process used for patients with serious or life-threatening diseases.

Suggested topics for a discussion of new regulatory pathways include the following:

a) Conditional approval of a new chemoprevention therapy under a paradigm similar to Subpart H

b) Programs in high risk populations utilizing novel selection criteria and surrogate endpoints of efficacy as the basis of approval, with the validation of surrogate endpoints of efficacy through long-term follow-up as a post-marketing commitment

c) Estimation of risk-benefit ratio in a lower-risk group leading to conditional approval based upon the risk-benefit ratio observed for a higher-risk group

d) Identification of different patient groups for whom the risk-benefit ratio is acceptable for full approval, for conditional approval, or for further study

6) Issues with Respect to Health Economics

Prevention is an important public health concern. Its costs, benefits and risks are therefore important to discuss for many reasons including: 1) to allow for the projection of the costs and benefits of prevention programs; 2) to prioritize among development programs and help determine whether a particular program should be funded or not, and if so by whom; and 3) to allow the emergence of an environment which is conducive to innovation and investment in prevention programs.

Many of the issues specific to prevention programs stem from the fact that costs are generally high, benefits occur late in time, and benefits accrue to a specific population which may or may not have borne its cost.

Suggested topics for a discussion of health economic topics include the following:

a) Value of future costs and benefits in relation to present costs and benefits

b) Interpretation of the outcomes of such economic analysis

c) Benchmarks for funding decisions

d) Cost-benefit assessment of prevention therapies

   i) Role of payers in determining patient eligibility for treatment

   ii) Effect of risk stratification on patient insurability

Sincerely,

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